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Risk Factors Associated with Multidrug-Resistant Tuberculosis

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ABSTRACT

Background: *Multi-drug resistant tuberculosis (MDR-TB), a form of TB resistant to isoniazid and rifampin , is considered as a major threat to TB control worldwide. Moreover, the infectivity of MDR-TB is similar to that of non-MDR TB. This study aims to find the risk factors associated with the development of MDR-TB among TB patients admitted to Masih Daneshvari Hospital, the national referral center for tuberculosis and lung diseases.*

Materials and Methods: *The national referral institute for tuberculosis and lung diseases in Tehran (NRITLD) receives all the MDR-TB cases from all over the country. Based on this criterion alone, forty-eight pulmonary MDR-TB patients who were referred to this center between 2002 and 2005 were included in this study. For the purpose of comparison, 234 patients diagnosed with pulmonary TB were also selected randomly as the control group. The two groups were compared based on 102 demographic and clinical variables. These variables included age, sex, nationality, drug and opium use, method of referral, symptoms and etc.*

Results: *Immigration and refugee status as well as history of anti-TB medication were found to be the most significant among the risk factors associated with MDR-TB. Also, 95.8% of the MDR-TB cases reported a previous history of anti-TB medication. This number was 23.1% in the non-MDR group. MDR-TB was more prevalent among the Afghan patients; out of a total of 78 Afghan patients, 22 (46.8%) composed the MDR-TB category, whereas, 56 (23.9%) Afghan patients belonged to the non-TB category.*

All MDR-TB patients had positive smears whereas 13.2% of non-MDR-TB patients had negative smears. Dyspnea and weight loss were among other significant variables. History of close contact, diabetes, smoking, drug use, fever, and BCG scar in both MDR TB and non-MDR-TB groups were among the insignificant variables found in this study.

Conclusion: *The limited sample size and location of the study may have resulted in insignificant variables. However, based on the obtained data, patient's status as an immigrant or a refugee is an important risk factor for both MDR and non-MDR TB and is of particular concern in the growing trend of MDR-TB.* ***(Tanaffos 2009; 8(3): 17-21)***

Key words: *Tuberculosis, Multidrug-resistant, Isoniazid, Rifampin*

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INTRODUCTION

According to the latest World Health Organiztion (WHO) report on TB, more than 8.8 million people are affected by TB annually and approximately 2 million related deaths occur every year. Meanwhile, the escalating incidence of drug-resistant tuberculosis has now turned into one of the major health concerns worldwide.

Multi-drug resistant tuberculosis (MDR-TB) is defined as a concomitant resistance to isoniazid and rifampin with or without resistance to other drugs. Erratic and infrequent consumption of anti-TB drugs is now believed to be one of the main causes of resistance development. The resistant infection may arise in an individual who has received inadequate or irregular treatment or alternatively be transmitted directly from an individual to another (1). Currently, MDR-TB is considered as one of the most important threats to TB control worldwide. Moreover, the infectivity of MDR-TB is similar to that of non-MDR TB (2-4).

Many studies have reported that poverty, lack of appropriate knowledge, and crowded living conditions are among the factors responsible for the development of MDR-TB (5, 6). In studies performed in the United States, recent immigrants from developing countries comprised a growing percentage of TB notifications (7- 10).

This study seeks to identify the risk factors responsible for the development of MDR-TB among TB patients admitted to the sole national tuberculosis referral center in Iran.

MATERIALS AND METHODS

Setting: This retrospective study was conducted at Masih Daneshvari Hospital, the national referral center for tuberculosis and lung diseases (NRITLD) in Tehran, Iran.

Inclusion Criteria: According to the Iran's national TB program (NTP), all patients who are considered as WHO CAT II regimen failures are referred to our center and should be suspected for MDR-TB infection. Only cases with definitive diagnosis of MDR-TB hospitalized in this hospital during the years 2002-2005 were enrolled in this study. A total of 48 cases were included in this study. For the purpose of comparison, 234 patients diagnosed with non-MDR pulmonary TB who were hospitalized and treated at our hospital during the same period of time were also randomly selected and comprised the control group.

Method: The two groups of MDR-TB and drug sensitive TB were compared in our study based on demographic and clinical variables. These variables included age, sex, nationality, drug and opium use, method of referral, symptoms and etc. In this regard, patients' medical records were evaluated. Statistical analysis of the collected data was performed using SPSS ver. 11.5 software. The Chi-square test was used for nominal variables, and whenever necessary, the Fisher's exact test was utilized. We also used the Student's *t*-test and the Mann-Whitney U-test for variables with normal distribution and abnormally distributed data, respectively. A p-value <0.05 was considered statistically significant.

The Scientific and Ethics Committee of the NRITLD approved the study protocol.

RESULTS

The mean age of patients was 43.51 ± 18.4 yrs in the MDR-TB and 49.6 ± 21.1 years in the non-MDR-TB groups. No significant difference was found between the two groups in terms of age, sex, level of education, smoking and drug abuse (Table 1).

In the relative analysis of the nationality of MDR-TB patients compared to non-MDR-TB cases (p-value $\leq .002$), it was found that out of a total of 78 Afghan patients, 22 (46.8%) composed the MDR-TB category whereas 56(23.9%) belonged to the non-MDR-TB category. Thus, MDR-TB was found to be

more prevalent among Afghan patients. Among Iranians with a total number of 201 cases, non-MDR-TB with 177 cases (75.6%) was more common than MDR-TB cases with 24 patients (51.1%). Also, 2.1% of the data belonged to a case from Bangladesh.

Table 1. Comparison of characteristics of patients with MDR-TB and non-MDR-TB

Group		MDR-TB	Non – MDR-TB	p-value
Age		43.51±18.4	49.6±21.1	0.078
Sex	Male	28(58.3%)	116(49.8%)	0.23
	Female	20(41.7%)	117(50.2%)	
Nationality	Iranian	24(51.1%)	177(76%)	0.002
	Afghan	22(46.8%)	56 (24%)	
Educated	Yes	13(27.7%)	63(26.9%)	0.917
	No	34(72.3%)	171(73.1%)	
Smoking	Yes	37(78.7%)	178(76.1%)	0.695
	No	10(21.3%)	56(23.9)	
Drug abuse	Yes	5(10.6%)	31(13.2%)	0.625
	No	42(89.4%)	203(86.8%)	
History of close contact	Yes	34(72.3%)	194(82.9%)	0.091
	No	13(27.7%)	40(17.1%)	
History of anti-TB medication	Yes	45(95.7%)	54(23.1%)	0.001
	No	2(4.3%)	180(76.9%)	
Sputum smear	Positive	45(95.7%)	190(81.2%)	0.014
	Negative	2(4.3%)	44(18.8%)	

Interestingly, our data demonstrated that positive history of previous anti-TB medication was significantly higher in MDR-TB group compared to non-MDR-TB controls. (p-value ≤ .001); 95.8% of MDR-TB cases reported a positive history of anti-TB medication. This number was 23.1% in the non-MDR group.

Another notable finding of our study was the statistically significant difference in sputum smear results between the MDR-TB and non-MDR-TB groups (p-value≤0.014). All MDR-TB patients except two (95.7%) had positive sputum smears for acid fast bacilli (AFB) whereas 81.2% of non-MDR-TB patients had positive smears.

Dyspnea was another significant variable. It was found to be more common among MDR TB cases (85.1%) than non MDR TB patients (68.4%) (p-value ≤0.021).

History of close contact and diabetes in both MDR and non MDR-TB groups were among the insignificant variables found in this study. Diabetes was more common in the non MDR-TB group (9.0% versus 6.4%). Other insignificant variables were smoking, drug use, fever, and BCG scar in both MDR-TB and non MDR-TB groups.

DISCUSSION

This study is one of a few conducted in the region aiming to identify the risk factors for MDR-TB infection.

Evaluation of the nationality of MDR and non MDR TB cases as a significant variable showed that the MDR TB group was consisted mostly of Afghans compared to non MDR-TB group which was mostly consisted of Iranian patients. A large fraction of the Afghan population living in Iran consists of refugees who have moved to Iran due to the unstable political and economical situation of their homeland country (11). The fact that most of these patients are refugees could be a possible risk factor for the development of resistance due to incomplete and irregular treatment of tuberculosis in them.

Espinal's study on the global situation of MDR TB demonstrated that in the developed countries where MDR TB is not a major public health hazard, the disease was still present among immigrants, refugees, and the homeless (12,13).

In addition, a study done by Faustini et al. has shown that cases among recent immigrants from developing countries comprised a growing percentage of TB notifications. Many cases were reported to be drug resistant and multi drug resistant

(14). Further researches in this regard and a more comprehensive TB control program can help overcome this issue considering the fact that both Iran and Afghanistan are among high burden countries in regard to TB.

A likely rationale for the higher rate of MDR-TB among Afghans is that although our center is a referral center even for Iranians, most Afghan patients who have had treatment failure or problems in their medication are referred to our center. It is noteworthy that in another study addressing the treatment outcome of MDR-TB patients in Iran, we found that the mortality rate was significantly higher among Iranians with MDR-TB compared to Afghan patients. This may raise the possibility of different virulence of various infective strains of Mycobacterium tuberculosis responsible for MDR-TB in the two communities (15).

History of anti-TB medication in MDR and non MDR-TB cases as another significant variable gives room for discussion. The Global Project on Anti-Tuberculosis Drug Resistance Surveillance showed that the median prevalence of MDR strains in new cases was only 1% in comparison to the 9.3% prevalence in the previously treated cases. The report states the need for separate data on MDR-TB by region. In this study we have demonstrated that 95.8% of MDR TB cases had a history of anti-TB medication but only 23.1% of the non-MDR TB cases had such history. These numbers showed a similar relationship between the two studies. A positive history of anti-TB medication is more common among MDR TB cases rather than the non-MDR TB patients. A study by Faustini et al. has shown that previous anti-TB treatment was the strongest determinant of MDR-TB in Europe (1).

In a study done by Bashar et al. on the increased incidence of multi-drug resistant tuberculosis among diabetic patients it was revealed that the proportion of MDR-TB cases was higher among those with diabetes resulting in a significant association between the two (16). Diabetes was shown to be a risk factor for non MDR-TB cases turning into MDR TB. Our study, however, showed no significant association between diabetes and MDR TB. In the present study it was demonstrated that diabetes was actually not a risk factor for the MDR-TB group.

Although the small sample size in our study and the nature of our hospital as a referral center may have influenced the results and the definitive conclusion, this study yields several interesting findings. Based on the obtained data, nationality is an important risk factor for both non MDR and MDR-TB especially MDR-TB. This may be attributed to several possible rationalizations including the problems associated with refugees and immigrants, the effect of referring complicated Afghan TB cases to Iran and possibly different resistant strains of MTB in the two ethnicities. However, this issue merits further investigations to propose a more vivid justification. As it has been severally depicted in other reports worldwide, positive history of anti-TB medication is also a very important determinant of acquiring MDR TB. Hence, it should be conveyed that more meticulous administration of anti-TB medication as well as more efficient follow-ups are required to prevent development of resistance to anti-TB agents due to mono-therapy or irregular anti-TB treatment.

Surprisingly, positive history of close contact with an identified TB patient did not reveal significant difference between MDR-TB and non-MDR-TB cases.

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